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Case report

Alteration of the lung parenchyma associated with autoimmune hepatitis

K. Kayser[1], K. Paul[2], D. Feist[2], W. Hofmann[3], L. Wille[2], and H.-J. Gabius[4]

[1] Department of Pathology, Thoraxklinik, Amalienstrasse 5, W-6900 Heidelberg, Federal Republic of Germany
[2] Pediatric Hospital and [3] Institute of Pathology, University of Heidelberg, W-6900 Heidelberg, Federal Republic of Germany
[4] Max-Planck-Institute for Experimental Medicine, Department of Chemistry, Hermann-Rein-Strasse 3, W-3400 Göttingen, Federal Republic of Germany

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Summary. The clinical history, radiological and histomorphological alterations of the lung parenchyma associated with chronic active autoimmune hepatitis are described. A 6-month-old female infant developed chronic active autoimmune hepatitis associated with autoimmune haemolytic anaemia. She was treated with immunosuppressive drugs, including steroids, for more than 6 years and developed symptoms and radiological signs of interstitial pneumonitis 4 years after onset of the autoimmune hepatitis. Associated bronchiectasis was detected 1 year later. No abnormalities of lung defence mechanisms could be demonstrated. Resection of the sixth left segment and of the basal parts of the left lower lobe revealed honeycombing with changes in the lung parenchyma which included chronic interstitial pneumonitis with multinucleate giant cells, seen predominantly in the distal airways, marked diffuse interstitial mononuclear infiltrates and mild diffuse interstitial fibrosis as well as bronchiectasis and organizing pneumonia. Granulomatous lesions, angiitis and necrotic areas were absent. Immunohistochemistry for immunoglobulins was negative for IgA, IgG and IgM and positive for IgD in the multinucleate giant cells. A strong positive reaction to HLA-DR-specific monoclonal antibody was noted, whereas no specific sugar receptors (endogenous lectins) could be detected by use of biotinylated glyconeoproteins.

Key words: Autoimmune hepatitis – Chronic interstitial pneumonitis – Autoimmune haemolytic anaemia – Endogenous lectins

Offprint requests to: K. Kayser

Introduction

Chronic liver disease may involve the lung via abnormal communications between the portal and pulmonary veins (Turner-Warwick 1968) or by changes in the lung caused by similar biochemical abnormalities to those in the liver parenchyma. The pathways of fibrogenesis in the lung parenchyma are still not known. However, there is evidence that activation of neutrophils and alveolar macrophages with IgA and IgG immune complexes may enhance the lung injury (Warren et al. 1987). In addition, blood-borne factors such as fibroblast growth factor are produced by lymphocytes, macrophages and platelets, and may be responsible for initiating fibroblast growth and collagen production (Adamson et al. 1988).

Chronic interstitial pneumonias associated with hypergammaglobulinaemia, hypogammaglobulinaemia, and autoimmune disorders have been described. In adults, they are manifest morphologically in the form of so-called lymphoid interstitial pneumonitis (LIP) (Liebow and Carrington 1973; Strimlan et al. 1978). Desquamative interstitial pneumonitis (DIP), a further entity of chronic interstitial lung diseases, has been reported to be associated with a variety of other major illnesses in children, including acute and chronic glomerulonephritis, ventricular septal defect, patent ductus arteriosus, tuberculosis, trisomy 21 and seborrhoeic dermatitis (Stillwell et al. 1980; Valdivia et al. 1977). Dreisin et al. (1978) reported circulating immune complexes and deposits of IgG and complement in the alveolar walls of patients with idiopathic interstitial pneumonitis, suggesting an immune mechanism for the disorder.

We report the clinical, radiological and histomorphological findings in a patient who suffered from congeni-

tal autoimmune hepatitis for several years and who later developed severe changes in the lung parenchyma.

Case report

Clinical history. A mature female infant developed haemolytic anaemia and symptoms of subacute hepatitis at the age of 6 months. Liver biopsy revealed findings consistent with chronic active autoimmune hepatitis. Fibrosis was absent, but several multinucleate giant cells were noted near to the central veins and in the portal fields. The patient was treated with immunosuppressive therapy including prednisone and Imurek. Stopping therapy invariably resulted in recurrent flare-up of the liver inflammation. The patient developed respiratory symptoms at the age of 4 years including a dry cough, shortness of breath during exercise, and rales. Marked progression of pulmonary symptoms was seen by the age of 5 years. Chest radiographs revealed increased diffuse densities in the left lower lung and patchy bilateral parahilar densities. The radiological findings were consistent with bronchiectasis, predominant in the sixth and tenth left segments. Lung function test revealed moderate diminished restrictive ventilation (vital capacity 1.1. l). Despite intensive physical and antibiotic therapy, progressive decrease of the lung function was noted. In addition, recurrent bilateral pleural effusions and atelectasis of the left lower lobe were seen. The scintigram of both lungs revealed diminished perfusion and ventilation, predominant in the left lower lobe.

Chest radiographs performed at age of 6 years showed bilateral interstitial markings with parapneumonic reaction of the pleura. Increased interstitial infiltrates were seen in the right paramediastinal and paracardial areas and in the left retrocardial space. Bronchography performed at the age of 7 years revealed bronchiectasis and atelectasis of the left lower lobe (Fig. 1). Pleural effusions were noted prior to resection of the left lower lobe.

Cilial functions of the bronchial epithelial cells were found to be normal as were the functions of lymphocytes and granulocytes (normal chemotaxis, normal subpopulations of lymphocytes, normal activiation of lymphocytes). Immunoglobulins in the serum were slightly increased (IgA 329 mg/ml; IgM 148 mg/ml; IgG 1230 mg/ml). Autoagglutination was seen against antigens of erythrocytes (positive Coombs' test, anti-IgG, anti-C3). Resection of the left lower lobe and of the sixth left segment was performed in order to cure the chronic pulmonary infection.

Pathology. The formalin-fixed, paraffin-embedded specimens were stained with haematoxylin and eosin periodic acid-Schiff, Sirius red and Giemsa. The neoglycoproteins used consisted of specific sugars bound to biotinylated carrier proteins (bovine serum albumin). The monoclonal antibodies and the neoglycoproteins were applied to 4–6 μm sections by use of the peroxidase-antiperoxidase technique. The following antibodies were used: IgA, BS5 (Biotest, Dreieich, FRG); IgD, Biotrend (Cologne, FRG); IgG, BS16 (Biotest); IgM, BS7 (Biotest); HLA-DR, LN3 (Biotest). Positive and

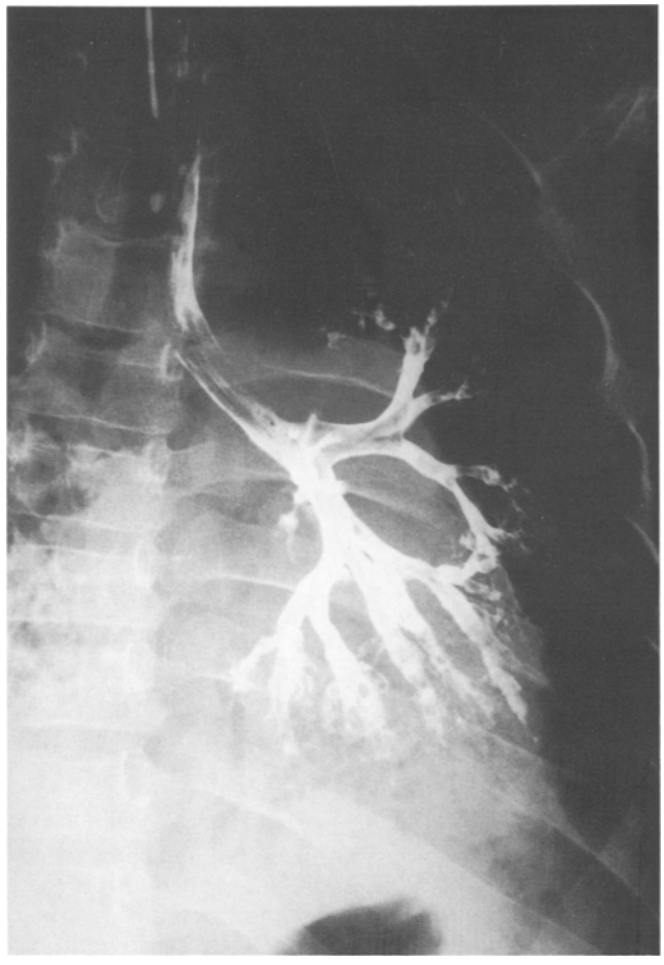

Fig. 1. Bronchography of the left lower lobe showing bronchiectasis and destruction of the peripheral lung parenchyma

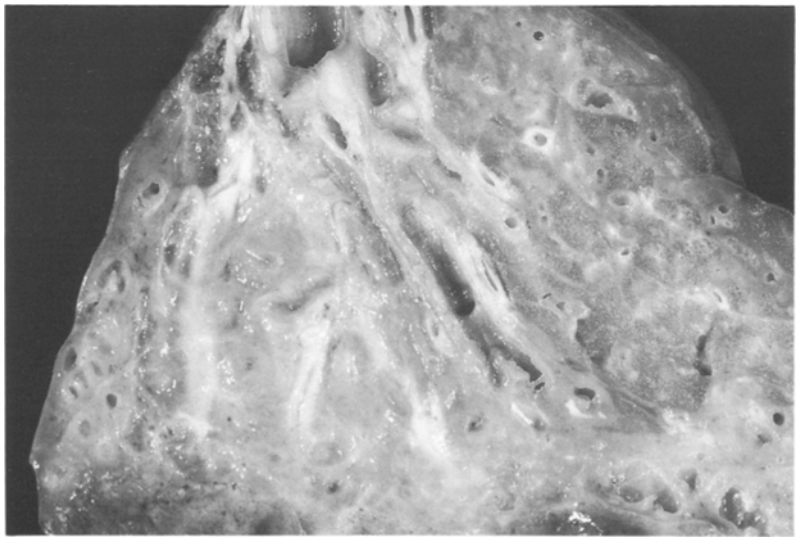

Fig. 2. Macroscopic image of the left lower lobe, which shows bronchiectasis, interstitial fibrosis and focal honeycombing

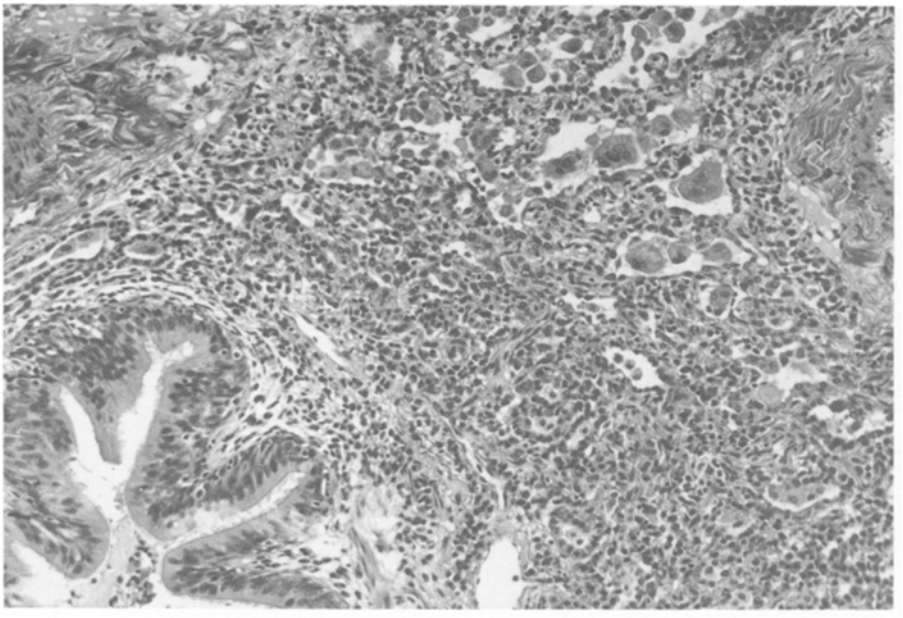

Fig. 3. Microphotograph showing dense interstitial inflammatory infiltrates, hyperplasia of the bronchial mucosa and multinucleate intra-alveolar giant cells. H&E, ×120

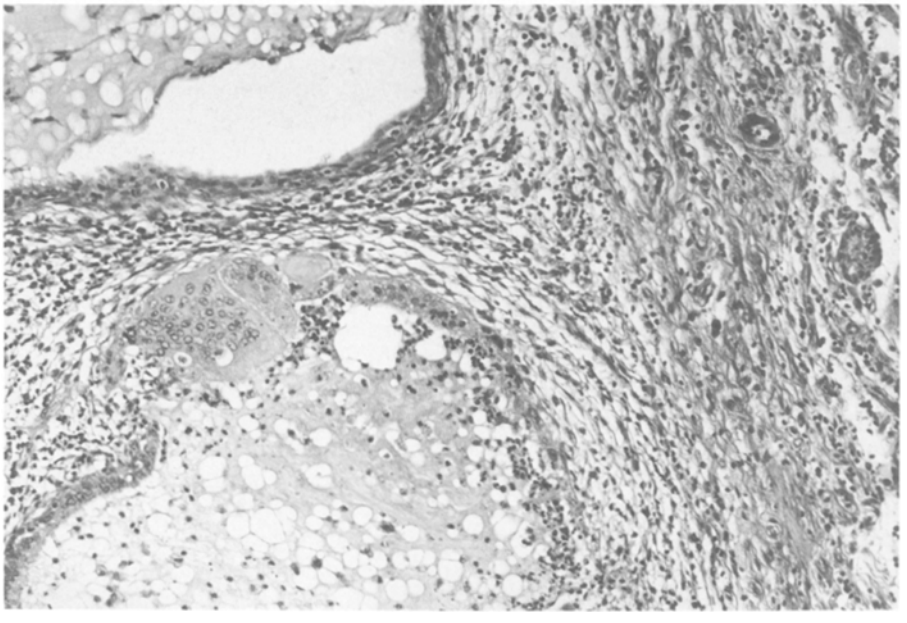

Fig. 4. Microphotograph showing bronchiectasis of medium-sized bronchi with severe surrounding fibrosis. The bronchial mucosa displays atrophy and focal multinucleate giant cells. H&E, ×120

negative controls were performed as usual. The procedures are described in detail elsewhere (Kayser et al. 1991).

The liver biopsy showed a preserved structure of the liver parenchyma and normal portal tract/hepatic vein relationships. The sinusoidal lining cells were fairly prominent, whereas the bile ducts and the hepatic artery branches were unremarkable. Numerous multinucleate giant cells intermingled with moderate eosinophilic and neutrophilic granulocytes were seen adjacent to the central veins and less numerous to the portal tracts. Immunohistochemically, IgA and IgM were absent. IgD was present in giant cells; HLA-DR was negative. Of the endogenous lectins, alpha-galactose, beta-galactose, *N*-acetylglucosamine, fucose, lactose, and mannose were all negative. These histomorphological findings are consistent with chronic active autoimmune hepatitis.

The left lower lobe measured 10 × 5 × 5 cm (70 g). Severe bronchiectasis of the proximal bronchi was noted as well as marked peribronchial fibrosis. Several pseudocysts measuring up to 1 cm in maximum diameter were present. Focal honeycombing was seen in the central and peripheral areas of the lobe (Fig. 2). Hyperplastic bronchial mucosa was noted in the small and medium sized bronchi. The adjacent lung parenchyma was altered by mononuclear interstitial inflammatory infiltrates and mild hyperplasia and hypertrophy of the cells of the alveolar lining (Fig. 3). Some of the smaller bronchi and related distant airways had been replaced by fibrotic scars. The larger and medium-sized bronchi showed extensive bronchiectasis with some squamous metaplasia. Multinucleate giant cells were found focally in the smaller bronchi and bronchioles, replacing the epithelial cells in the bronchial mucosa (Fig. 4). The submucosal glands were destroyed by lymphocytic and plasmocytic infiltrates. Distal airways contained numerous multinucleate giant cells, which were found alone in the alveolar ducts and alveoli (Fig. 5), partly connected with the cells of the alveolar lining. Aggregations of macrophages were infrequent. The interalveolar septa were diffusely infiltrated by mononuclear infiltrates of histiocytes, lymphocytes and plasma cells. Marked interstitial fibrosis, present in the lung areas with honeycombing, was not seen in these areas. The result of immunohistochemistry showed IgD to be present and HLA-DR (LN3) to be positive.

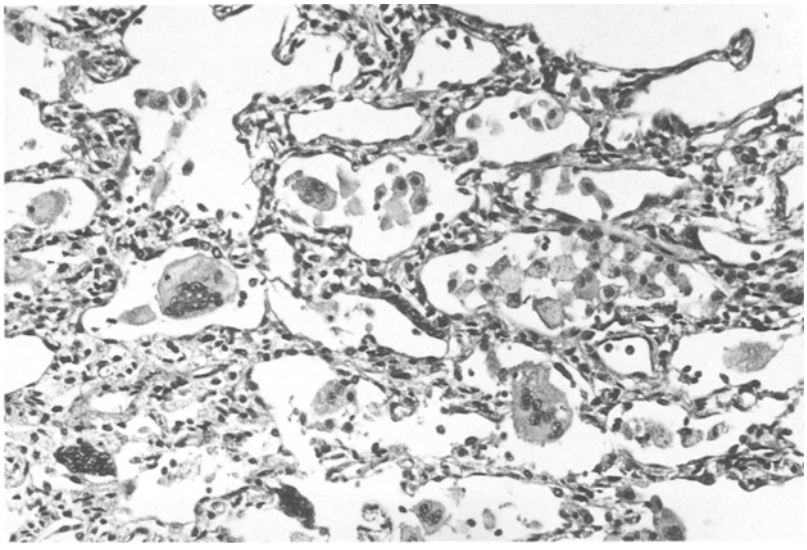

Fig. 5. Microphotograph of peripheral lung parenchyma showing diffuse interstitial mononuclear infiltrates and numerous multinucleate giant cells in the alveoli. H&E, ×140

The multinucleate giant cells were the main site of staining by IgD-specific monoclonal antibody. Analysis of the peripheral lung parenchyma for endogenous lectins with neoglycoproteins was negative for the following sugar-binding capacities: alpha-galactose, beta-galactose, *N*-acetylglucosamine, fucose, lactose and mannose. The findings correlate with those obtained in the liver biopsies, which were also negative under the same experimental conditions for the synthetic probes used.

Discussion

This case is characterized by development of autoimmune hepatitis in early childhood and subsequent progressive involvement of the lung parenchyma in the following years. The disturbance of the immune system was probably induced by autoantibodies against antigens of erythrocytes (positive Coombs' test, anti-IgG, and anti-C3). Although a number of serum autoantibodies have been reported in chronic liver diseases (Doniach and Walker 1972; Glynn 1972), their role in chronic liver cell injury is still questionable (MacSween et al. 1979).

Histomorphological alterations of the liver parenchyma revealed active hepatitis with multinucleate giant cells, mainly present near to the central veins and to the portal fields. Similar multinucleate giant cells were noted in the lung parenchyma (Fig. 5).

Although interstitial pneumonitis is a rare disease in childhood several reports describe interstitial changes of the lung parenchyma in children (Laraya-Cuasay and Hughes 1988). The reported cases revealed either LIP (Churg et al. 1981), or DIP (Liebow et al. 1965; Stillwell et al. 1980). Fourteen of 28 cases with DIP developed symptoms within the first year of life. Two of the reported cases were siblings (Stillwell et al. 1980). No pathological correlations between DIP in childhood and other diseases were detected. In contrast, LIP in childhood has been reported to be associated with defects in immune status (Yoshizawa et al. 1984). These defects include monoclonal and polyclonal gammopathies, dysproteinaemias, chronic active hepatitis with renal tubular syndrome, myasthenia with pernicious anaemia, juvenile rheumatoid arthritis, and manifestation of chronic graft versus host disease after bone marrow transplantation. Organ specific autoimmune lesions have also been described in various animal models (Hayashi et al. 1989; Passwell et al. 1988).

The morphological findings in the liver and the lung parenchyma of our patient suggest the following conclusions to us. The inflammatory infiltrates in both organs are characterized by multinucleate giant cells, which contain IgD in both organs. The inflammatory infiltrates do not express binding capacities to a variety of applied neoglycoproteins in both organs. These tools are important in the detection of those endogenous lectins implicated as those contributing to the host defence system (Gabius 1991). Inflammatory infiltrates in human lung parenchyma due to non-specific (bacterial) agents normally express positive binding capacities to fucose, lactose and mannose (Kayser et al. 1991). The negative reaction to neoglycoproteins suggests that the observed abnormalities in the lung parenchyma are not related to immunosuppressive therapy. The application of cytostatic and immunosuppressive drugs usually induces strong binding capacities for neoglycoproteins (Kayser et al. 1991).

Non-specific activation of the macrophage system, which is characterized by expression of HLA-DR, is present in the lung in this case, and is also evident in the liver parenchyma. The inflammatory process is, therefore, active.

The causative agent of the morphological alterations of the liver and the lung parenchyma is probably the same in this case and may be related to autoimmune antibodies. Although there are many causes for the generation of multinucleate giant cells (including measles, tuberculosis and so on) it seems unlikely that giant cells induced by different causes express the same binding capacities to various neoglycoproteins (Kayser et al. 1991). This assumption warrants further experimental attention.

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